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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,050	06/29/2007	Kazuya Hosokawa	JCLA21671	3526

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4 VENTURE, SUITE 250
IRVINE, CA 92618

EXAMINER	
TSAY, MARSHA M	
ART UNIT	PAPER NUMBER
1656	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,050	HOSOKAWA ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-57* is/are pending in the application.

4a) Of the above claim(s) *5,21-36,40,41,44,49 and 51-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-20,37-39,42,43,45-48 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :06.28.07; 08.01.07; 11.20.07; 06.02.09.

DETAILED ACTION

Applicant's election of Group I, claims 1-20, 37-48, 50-57, to the species blood coagulation factor 13, in the reply filed on March 12, 2010, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 6-7 are canceled. Claims 5, 21-36, 40-41, 44, 49, 51-57 have been withdrawn by Applicants. Claims 1-4, 8-20, 37-39, 42-43, 45-48, 50, to the species blood coagulation factor 13, are currently under examination.

Priority: The request for priority to JAPAN 2004-080950, filed March 19, 2004, is acknowledged. A certified copy of the foreign priority document has been filed in this case on September 18, 2006, and is in a non-English language.

Claim Objections

Claims 43, 48 are objected to because of the following informalities: claim 43 is objected to because there are no units recited for the molecular weight of polyethylene glycol; in claim 48, the acronym PAR1 should be spelled out in full the first time that it is recited in the claims, i.e. protease activated receptor (PAR1). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8-20, 37-39, 42-43, 45-48, 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified thrombin protein consisting an A chain and a B chain, wherein the B chain has an amino acid sequence in which two or more kinds of active center amino acids selected from the group consisting of serine at position 205, glycine at position 203, aspartic acid at position 99, and histidine at position 43 in the amino acid sequence of a thrombin B chain are substituted and wherein said modified thrombin cleaves a thrombin substrate at a ratio of 10% or less, does not reasonably provide enablement for a thrombin derivative comprising an A chain and a B chain, wherein the B chain has an amino acid sequence in which two or more kinds of active center amino acids selected from the group consisting of serine at position 205, glycine at position 203, aspartic acid at position 99, and histidine at position 43 in the amino acid sequence of a thrombin B chain are substituted and wherein said modified thrombin cleaves a thrombin substrate at a ratio of 10% or less. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art to ascertain which derivatives of thrombin would cleave a thrombin substrate at a ratio of 10% or less. Wild-type thrombin consists of two polypeptides (A and B chains) that are linked by a single disulfide bond. It should be noted that the use of open claim language "comprising" allows the instant thrombin derivative to have additional amino

acid residues. Thus there could be thousands of thrombin derivatives which contain amino acid additions, modifications, etc. Thus for the instant claimed invention, it would require an undue burden of experimentation for a skilled artisan to determine exactly which derivatives were active.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

On page 20, paragraph [0021] of the instant specification discloses that the instant thrombin derivative comprises an A chain and a B chain, and in which a particular amino acid in the B chain is substituted. As already noted, the use of open claim language "comprising" allows the instant thrombin derivative to have additional amino acid residues. In the instant case the

quantity of experimentation would be large since there are myriad substitutions, additions, or insertions to choose from. The amount of guidance in the specification is minimal with regard to thrombin derivatives that cleave a thrombin substrate at a ratio of 10%. The specification appears to have support for modified thrombin proteins consisting of an A chain and a B chain, wherein the B chain is substituted at positions 205, 203, 99, and 43, that can cleave a thrombin substrate at a ratio of 10%. However, the specification provides insufficient guidance as to which thrombin derivatives comprising an A chain and a B chain, wherein the B chain is substituted at positions 205, 203, 99, and 43, that can cleave a thrombin substrate at a ratio of 10%. The nature of the invention is such that many different peptides that are substantially similar to thrombin may or may not have biological activity. In general, the art of making modified proteins with a desired function is very unpredictable in nature. The specification provides insufficient guidance as to the specific positions and regions of the sequence(s) that can be predictably modified and which regions are critical. Without such guidance, the change which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986). It is known in the art that an amino acid sequence identity of 50% does not guarantee structural similarity (Yuan et al. 1998 Proteins 30: 136-143), and that even a single point mutation in a polypeptide sequence can lead to surprising alteration in protein structure and activity (Sergel et al. 2000 J Virol 74: 5101-5107). The relative level of skill in this art is very high. The predictability as to what substantially similar protein will have which activity is zero.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

Claims 1-4, 8-20, 37-39, 42-43, 45-48, 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to thrombin derivatives comprising an A chain and a B chain, wherein the B chain has an amino acid sequence in which two or more kinds of active center amino acids selected from the group consisting of serine at position 205, glycine at position 203, aspartic acid at position 99, and histidine at position 43 in the amino acid sequence of a thrombin B chain are substituted and wherein said modified thrombin cleaves a thrombin substrate at a ratio of 10% or less.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical, and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001,

see especially page 1106 column 3). *Vas-Cath Inc. V. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."*

The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." As stated above, thrombin derivatives comprising an A chain and a B chain, wherein the B chain has an amino acid sequence in which two or more kinds of active center amino acids selected from the group consisting of serine at position 205, glycine at position 203, aspartic acid at position 99, and histidine at position 43 in the amino acid sequence of a thrombin B chain are substituted and wherein said modified thrombin cleaves a thrombin substrate at a ratio of 10% or less. On page 20, paragraph [0021] of the instant specification discloses that the instant thrombin derivative comprises an A chain and a B chain, and in which a particular amino acid in the B chain is substituted. As already noted, the use of open claim language "comprising" allows the instant thrombin derivative to have additional amino acid residues. Therefore, the skilled artisan cannot necessarily envision the detailed structures of ALL of the derivatives of thrombin that cleaves a thrombin substrate at a ratio of 10% or less. Additionally, it should be noted that there is no function recited in the thrombin derivatives of claims 19-20. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 8, 10-11, 13-20, 37-38, 48, 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arcone et al. (1999 Biochimica et Biophysica Acta 1451: 173-186; IDS 06.28.07) in view of current practice in protein design, as evidenced by Wells (1990 Biochemistry 29(37): 8509-8517). The Wells reference is cited as a reference to note that it was known in the art at the time of the invention that additive mutagenesis, where a series of single mutants each making a small improvement in function are combined, is a powerful tool in designing functional properties in proteins (Wells p. 8515).

For examination purposes, the instant claims have been interpreted as: a thrombin derivative comprising an A chain and a B chain, wherein the B chain has an amino acid sequence in which two or more kinds of active center amino acids selected from the group consisting of serine at position 205, glycine at position 203, aspartic acid at position 99, and histidine at position 43 in the amino acid sequence of a thrombin B chain are substituted. The functional limitations recited in claims 1-2, and their dependent claims have not been given patentable weight since said limitations are properties that would be present if two more kinds of the amino acids at positions 205, 203, 99, and 43 are substituted.

Arcone et al. disclose human thrombin mutants where single amino acid substitutions were introduced in the catalytic triad (H43N, D99N, S205A, S205T), in the oxy-anion binding

site (G203A) and in the anion binding exosite-I region (R73E) (p. 173). Arcone et al. further disclose that mutations S205A and G203A completely abolished the enzyme activity and that mutations H43N, D99N, and S205T dramatically impaired the enzyme activity toward a chromogenic substrate and fibrinogen (p. 173, p. 179, also Table I). Arcone et al. do not teach two or more substitutions selected from H43N, D99N, S205A or S205T, and G203A.

However, as evidenced by Wells, it is known that single amino acid substitutions can be combined so that their effects on a protein are cumulative (p. 8515).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Arcone et al. by combining the single amino acid substitutions of Arcone et al., H43N, D99N, S205A or S205T, and G203A, in view of what is known in the art about protein design (as evidenced by Wells) in order to make a modified thrombin protein that has decreased or no enzymatic activity (claims 1-4, 8, 10-11, 13-20, 37-38, 48, 50). The motivation to do so is given by Arcone et al. in view of Wells, which disclose that single amino acid substitutions at the catalytic triad disrupts the enzymatic activity of thrombin; therefore, it would be reasonable for one of ordinary skill to combine the single amino acid substitutions so that two or more substitutions selected from H43N, D99N, S205A or S205T, and G203A, are combined to make a modified thrombin protein that has the approximately no enzymatic activity.

Regarding the functional limitations recited in claims 1-4, 13-18, 48, said limitations have not been given patentable weight since said limitations are properties that would be present if two more kinds of the amino acids at positions 205, 203, 99, and 43 are substituted, as

disclosed by Arcone et al. in view of the state of the art in protein design (as evidenced by Wells).

Arcone et al. disclose human thrombin mutants; therefore, it would be reasonable for one of ordinary skill to know that the thrombin B chain of Arcone et al. is an amino acid sequence of a B chain of human wild-type thrombin (claims 37-38).

Arcone et al. disclose a liquid composition of the purified thrombin mutants; therefore, it would have been obvious to one of ordinary skill to know that said modified thrombin protein of Arcone et al. as evidenced by Wells can also be incorporated into a liquid composition (claim 50).

Claims 39, 42-43, 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arcone et al. (1999 Biochimica et Biophysica Acta 1451: 173-186; IDS 06.28.07) in view of Veronese (2001 Biomaterials 22: 405-417). The teachings of Arcone et al. are outlined above. Arcone et al. do not teach modifying a carboxyl group with polyethylene glycol (PEG).

Veronese et al. disclose that PEGylation of proteins enhances the therapeutic and biotechnological potential of proteins (p. 405). When PEG is properly linked to a protein, it modifies many of the protein's features while maintaining its biological functions, i.e. PEG increases the molecular size of the protein and can also reduce its degradation by proteolytic enzymes (p. 406). Veronese discloses general PEGylation chemistry to show that arginine residues and carboxyl groups on a protein can be modified, i.e. PEGylated (p. 410).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the multiple amino acid substituted thrombin mutant of Arcone et al.

by modifying the carboxyl groups of said thrombin mutant with PEG, as suggested by Veronese et al. (claims 39, 42-43, 45-46). The motivation to do so is given by Veronese et al., which disclose that PEG can be linked to a protein, i.e. arginine residues or carboxyl groups, to enhance its therapeutic and biotechnological potential.

Regarding the limitations of claims 43, 45-46, it would be reasonable for one of ordinary skill to want to determine the optimum molecular weight of the PEG and the number of carboxyl groups to be PEGylated in order to make a modified thrombin protein with the level of therapeutic and biotechnological potential that one of ordinary skill would like.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Arcone et al. (1999 Biochimica et Biophysica Acta 1451: 173-186; IDS 06.28.07) in view of Veronese (2001 Biomaterials 22: 405-417) in view of Roberts et al. (2002 Advanced Drug Delivery Reviews 54: 459-476). The teachings of Arcone et al. in view of Veronese are outlined above. Arcone et al. in view of Veronese do not teach PEGylating a carboxyl group of a glutamic acid at position 25 in the B chain.

Roberts et al. disclose that glutamic acid is a typical reactive amino acid that can be PEGylated (p. 461).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the multiple amino acid substituted thrombin mutant of Arcone et al. in view of Veronese by PEGylating a carboxyl group of a glutamic acid residue in said thrombin mutant, as suggested by Roberts et al. (claim 47). The motivation to do so is given by Roberts et al., which disclose that a typical reactive amino acid in PEGylation chemistry is glutamic acid;

therefore, it would be reasonable for one of ordinary skill to determine which residues on said thrombin mutant is best suited for PEGylation, i.e. glutamic acid residues on the B chain, including the one at position 25.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marsha M. Tsay/
Examiner, Art Unit 1656

June 23, 2010